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(21) International Application Number: PCT/GB93/00013 (22) International Filing Date: 7 January 1993 (07.01.93) (30) Priority data: 9200781.4 15 January 1992 (15.01.92) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : CARLING, William, Robert [GB/GB]; 15 The Colts, Thorley Park, Bishops Stortford, Hertfordshire CM23 4DL (GB). LEESON, Paul, David [GB/GB]; 127 Mawson Road, Cambridge, Cambridgeshire CB1 2DZ (GB). SMITH, Julian, Duncan [GB/GB]; 14 St. Regis, Chesterton Road, Cambridge, Cambridgeshire CB4 1BY (GB).		(74) Agent: THOMPSON, John; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: NITROQUINOLONE DERIVATIVES AS NMDA ANTAGONISTS (57) Abstract A class of optionally 4-substituted 3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline derivatives are selective non-competitive antagonists of NMDA receptors and/or are antagonists of AMPA receptors, and are therefore of utility in the treatment of conditions, such as neurodegenerative disorders, convulsions or schizophrenia, which require the administration of an NMDA and/or AMPA receptor antagonist.		

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- 1 -

Nitroquinolone derivatives as NMDA antagonists

This invention relates to a class of optionally
5 4-substituted 3-nitro-2-oxo-1,2,3,4-tetrahydroquinolines
which are selective non-competitive antagonists of N-
methyl-D-aspartate (NMDA) receptors. More particularly,
the class of compounds provided by the present invention
are ligands for the strychnine-insensitive glycine
10 modulatory site of the NMDA receptor and are therefore
useful in the treatment and/or prevention of
neurodegenerative disorders arising as a consequence of
such pathological conditions as stroke, hypoglycaemia,
cerebral palsy, transient cerebral ischaemic attack,
15 cerebral ischaemia during cardiac pulmonary surgery or
cardiac arrest, perinatal asphyxia, epilepsy,
Huntington's chorea, Alzheimer's disease, Amyotrophic
Lateral Sclerosis, Parkinson's disease, Olivo-ponto-
cerebellar atrophy, anoxia such as from drowning, spinal
20 cord and head injury, and poisoning by exogenous and
endogenous NMDA receptor agonists and neurotoxins,
including environmental neurotoxins.

By virtue of their NMDA receptor antagonist
properties, the compounds according to the present
25 invention are also useful as anticonvulsant and
antiemetic agents, as well as being of value in the
prevention or reduction of dependence on dependence-
inducing agents such as narcotics.

NMDA receptor antagonists have recently been
30 shown to possess analgesic (see, for example, Dickenson
and Aydar, Neuroscience Lett., 1991, 121, 263; Murray et al., Pain, 1991, 44, 179; and Woolf and Thompson, Pain,
1991, 44, 293) and anxiolytic (see, for example, Kehne et al., Eur. J. Pharmacol., 1991, 193, 283) effects, and the

- 2 -

compounds of the present invention may accordingly be useful in the management of pain and anxiety.

Compounds possessing functional antagonist properties for the NMDA receptor complex are stated in WO-A-91/19493 to be effective in the treatment of mood disorders, including major depression, bipolar disorder, dysthymia and seasonal affective disorder (cf. also Trullas and Skolnick, Eur. J. Pharmacol., 1990, 185, 1). The compounds of the present invention may consequently be of benefit in the treatment and/or prevention of such disorders.

The association of NMDA receptor antagonists with regulation of the dopaminergic system has recently been reported (see, for example, Werling et al., J. Pharmacol. Exp. Ther., 1990, 255, 40; Graham et al., Life Sciences, 1990, 47, PL-41; Hutson et al., Br. J. Pharmacol., 1991, 103, 2037; and Turski et al., Nature (London), 1991, 349, 414). This suggests that the compounds of the present invention may thus be of assistance in the prevention and/or treatment of disorders of the dopaminergic system such as schizophrenia and Parkinson's disease.

It has also been reported recently (see Lauritzen et al., Journal of Cerebral Blood Flow and Metabolism, 1991, vol. 11, suppl. 2, Abstract XV-4) that NMDA receptor antagonists block cortical spreading depression (CSD), which may thus be of clinical importance since CSD is a possible mechanism of migraine. The class of substituted 2-amino-4-phosphonomethylalk-3-ene carboxylic acids and esters described in EP-A-0420806, which are stated to be selective NMDA antaonists, are alleged thereby to be of potential utility in the treatment of inter alia migraine.

- 3 -

Excitatory amino acid receptor antagonists, including inter alia antagonists of NMDA receptors, are alleged in EP-A-0432994 to be of use in suppressing emesis.

5 Recent reports in the literature have also suggested a link between the neurotoxicity of certain viruses and the deleterious effects of these viruses on an organism caused by the potentiation of neurotransmission via excitatory amino acid receptors.
10 By virtue of their activity as antagonists of NMDA receptors, therefore, the compounds of the present invention may be effective in controlling the manifestations of neuroviral diseases such as measles, rabies, tetanus (cf. Bagetta et al., Br. J. Pharmacol., 1990, 101, 776) and AIDS (cf. Lipton et al., Society for Neuroscience Abstracts, 1990, 16, 128.11).

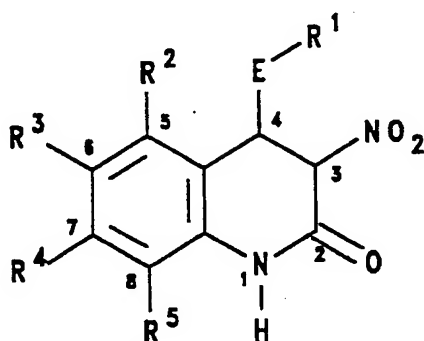
NMDA antagonists have, moreover, been shown to have an effect on the neuroendocrine system (see, for example, van den Pol et al., Science, 1990, 250, 1276;
20 and Urbanski, Endocrinology, 1990, 127, 2223), and the compounds of this invention may therefore also be effective in the control of seasonal breeding in mammals.

In addition, certain compounds of the invention are antagonists of 2-amino-3-hydroxy-5-methyl-4-
25 isoxazolepropionic acid (AMPA) receptors, also known as quisqualate receptors. An excitatory amino acid projection from the prefrontal cortex to the nucleus accumbens (a particular region of the forebrain possessing dopamine-sensitive neurones) is well known to
30 exist (see, for example, J. Neurochem., 1985, 45, 477). It is also well known that dopaminergic transmission in the striatum is modulated by glutamate (see, for example, Neurochem. Int., 1983, 5, 479), as also is the hyperactivity associated with presynaptic stimulation of

- 4 -

the dopamine system by AMPA in the nucleus accumbens (cf. Life Sci., 1981, 28, 1597). Compounds which are antagonists of AMPA receptors are therefore of value as neuroleptic agents.

5 The present invention accordingly provides a compound of formula I, or a salt or prodrug thereof:

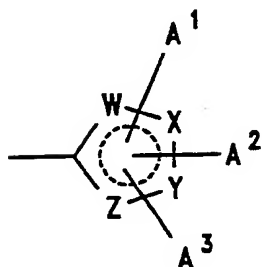


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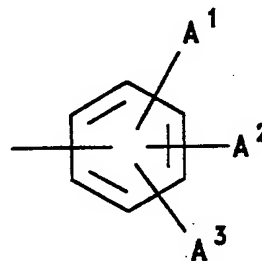
wherein

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

20 R^1 represents hydrogen, $-OR^a$, $-NR^aR^b$, $-CO_2R^a$, $-CONR^aR^b$ or a group of formula



or



30 in which the broken circle represents two non-adjacent double bonds in any position in the five-membered ring;

W, X, Y and Z independently represent oxygen, sulphur, nitrogen or carbon, provided that no more than one of W, X, Y and Z represents oxygen or sulphur, at

- 5 -

least one of W, X, Y and Z represents carbon and at least one of W, X, Y and Z is other than carbon;

A¹, A² and A³ represent one, two or three substituents (not exceeding the maximum number permissible by the disposition of heteroatoms in the five-membered ring), which substituents are independently selected from hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -SO₂NR^aR^b, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -COR^a, -CO₂R^a or -CONR^aR^b; or A¹ and A² or A² and A³ together represent the residue of an aromatic or heteroaromatic ring;

R², R³, R⁴ and R⁵ independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -SO₂NR^aR^b, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -COR^a, -CO₂R^a or -CONR^aR^b; or R² and R³, R³ and R⁴ or R⁴ and R⁵ together represent the residue of an aromatic or heteroaromatic ring; and

R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl and aryl(C₁₋₆)alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably

- 6 -

linked through carbon. Examples of suitable heterocyclic groups include C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl and heteroaryl(C₁₋₆)alkyl groups.

5 Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, n-propyl,
10 isopropyl, n-butyl and t-butyl.

 Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

15 Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

 Suitable cycloalkyl groups include groups
20 containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

 Suitable aryl groups include phenyl and naphthyl groups.

 Particular aryl(C₁₋₆)alkyl groups include
25 benzyl, phenethyl, phenylpropyl and phenylbutyl.

 Suitable heterocycloalkyl groups include piperidyl, piperazinyl and morpholinyl groups.

 Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl,
30 pyrazinyl, pyranyl, furyl, benzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, imidazolyl, oxadiazolyl and thiadiazolyl groups. Particular heteroaryl groups are pyridyl, furyl, benzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl and oxadiazolyl.

- 7 -

Particular heteroaryl(C₁₋₆)alkyl groups include indolylethyl, indolylpropyl and thienylethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C₁₋₆ alkyl, adamantyl, phenyl, halogen, C₁₋₆ haloalkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkoxy(C₁₋₆)alkoxy, aryloxy, keto, C₁₋₃ alkylenedioxy, nitro, cyano, carboxy, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, C₂₋₆ alkylcarbonyloxy, optionally substituted arylcarbonyloxy, C₂₋₆ alkylcarbonyl, optionally substituted arylcarbonyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, arylthio, amino, mono- or di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino and C₂₋₆ alkoxycarbonylamino(C₁₋₆)alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine.

The alkylene chain E may be, for example, methylene, ethylene, 1-methylethylene, propylene or 2-methylpropylene, preferably methylene. Alternatively, the group E may represent a single bond such that the moiety R¹ in formula I is attached directly to the tetrahydroquinoline ring system.

The five-membered heteroaromatic ring containing the ring atoms W to Z may be, for example, a furan, thiophene, pyrrole, oxazole, thiazole, isoxazole, isothiazole, oxadiazole or thiadiazole ring, in particular a furan, thiophene, pyrrole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole or 1,3,4-thiadiazole ring. Preferably the ring is a furan, thiophene, pyrrole, 1,2,4-oxadiazole or 1,2,4-thiadiazole ring.

The number of substituents A¹, A² and/or A³ present on the five-membered heteroaromatic ring

- 8 -

containing the ring atoms W to Z is one, two or three depending upon the disposition of heteroatoms in the heteroaromatic ring. Thus where, for example, the five-membered heteroaromatic ring is an oxadiazole or thiadiazole ring, only one substituent will be permitted; where, for example, the five-membered heteroaromatic ring is an oxazole or thiazole ring, one or two substituents will be permitted; and where, for example, the five-membered heteroaromatic ring is a furan, thiophene or pyrrole ring, one, two or three substituents will be permitted.

Suitable values for the groups A^1 , A^2 and/or A^3 include hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, optionally substituted aryl, optionally substituted aryl(C_{1-6})alkyl, halogen, cyano, trifluoromethyl, nitro, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{1-6} alkylthio, C_{2-6} alkenylthio, $-COR^a$ or $-NR^aR^b$, in which R^a and R^b are as defined above.

When R^1 in the compounds of formula I above represents a group of formula $-OR^a$, $-NR^aR^b$, $-CO_2R^a$ or $-CONR^aR^b$, the substituents R^a and R^b are suitably selected independently from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl and heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted.

Representative values of R^1 include hydrogen, methoxy, dimethylamino, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, phenylaminocarbonyl, benzylaminocarbonyl, dimethyl-aminocarbonyl, N-methyl-N-phenylaminocarbonyl and methyloxadiazolyl.

- 9 -

In a particularly preferred embodiment of the present invention, E represents a bond and R¹ represents hydrogen.

The benzo moiety of the tetrahydroquinoline ring system shown in formula I above preferably contains at least one non-hydrogen substituent. Particular substituents include halogen, cyano, trifluoromethyl, nitro, hydroxy, amino, carboxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio and C₂₋₆ alkoxy carbonyl. Suitably, R⁵ represents hydrogen and R², R³ and R⁴ independently represent hydrogen, halogen, nitro, amino or C₁₋₆ alkyl, provided that at least one of R², R³ and R⁴ is other than hydrogen. Preferably, R³ and R⁵ each represents hydrogen and R² and R⁴ independently represent hydrogen, nitro, amino, methyl or halogen, especially chlorine, provided that at least one of R² and R⁴ is other than hydrogen. In a preferred embodiment, R⁴ represents chlorine.

Where R² and R³, R³ and R⁴, R⁴ and R⁵, A¹ and A² or A² and A³ represent the residue of an aromatic or heteroaromatic ring, this is suitably an optionally substituted benzene, pyridine, thiophene, thiazole or thiadiazole ring. As optional substituents on the aromatic or heteroaromatic ring may be mentioned nitro, and C₁₋₆ alkoxy such as methoxy.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of formula I above include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g.

- 10 -

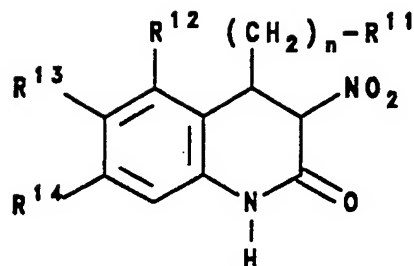
quaternary ammonium salts. Where appropriate, acid addition salts may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

One sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:

- 11 -



(IIA)

10 wherein

n is zero, 1, 2 or 3, preferably zero or 1;

R^{11} represents hydrogen, $-OR^{16}$, $-NR^{16}R^{17}$, $-CO_2R^{16}$ or $-CONR^{16}R^{17}$;

15 R^{12} , R^{13} and R^{14} independently represent hydrogen, halogen, cyano, trifluoromethyl, nitro, hydroxy, amino, carboxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio or C_{2-6} alkoxy carbonyl; and

20 R^{16} and R^{17} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted.

25 Examples of optional substituents on the groups R^{16} and/or R^{17} suitably include hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy and C_{2-6} alkoxy carbonyl-amino(C_{1-6})alkyl, especially hydroxy, methoxy, methoxymethoxy and *t*-butoxycarbonylaminomethyl.

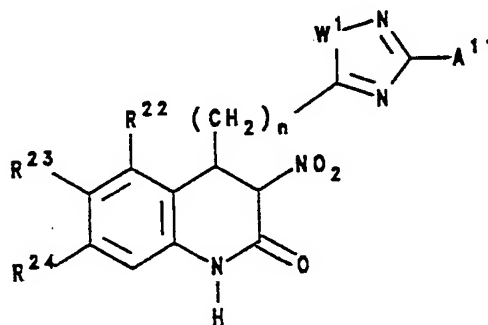
30 Particular values of R^{11} with respect to formula IIA include hydrogen, methoxy, dimethylamino, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, phenylaminocarbonyl, benzylaminocarbonyl, dimethylaminocarbonyl and *N*-methyl-*N*-phenylaminocarbonyl.

- 12 -

In a preferred embodiment, n is zero and R¹¹ is hydrogen. When R¹¹ is other than hydrogen, n is suitably other than zero and preferably 1.

Suitably, R¹², R¹³ and R¹⁴ are independently
 5 selected from hydrogen, halogen, nitro, amino and C₁₋₆ alkyl. Ideally, at least one of R¹², R¹³ and R¹⁴ is other than hydrogen. Preferably, R¹³ represents hydrogen, one of R¹² and R¹⁴ represents halogen or nitro, and the other of R¹² and R¹⁴ represents hydrogen, halogen
 10 or nitro. In a particular embodiment, R¹² and R¹³ each represents hydrogen and R¹⁴ represents halogen, especially chlorine.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB,
 15 and salts and prodrugs thereof:



(IIB)

wherein

n is zero, 1, 2 or 3, preferably 1;

W¹ represents oxygen or sulphur, preferably

oxygen;

30

A¹¹ represents hydrogen, halogen, cyano, trifluoromethyl, nitro, hydroxy, amino, carboxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyloxy, C₁₋₆ alkylthio, C₂₋₆

- 13 -

alkenylthio, C₂₋₆ alkylcarbonyl, arylcarbonyl or C₂₋₆ alkoxy carbonyl; and

R²², R²³ and R²⁴ independently represent hydrogen, halogen, cyano, trifluoromethyl, nitro, hydroxy, amino, carboxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio or C₂₋₆ alkoxy carbonyl.

Examples of suitable values for the group A¹¹ include hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyloxy, C₁₋₆ alkylthio, C₂₋₆ alkenylthio and arylcarbonyl. Particular values of A¹¹ include hydrogen, bromo, methyl, ethyl, isopropyl, vinyl, allyl, cyclopropyl, cyclopropylmethyl, phenyl, benzyl, allyloxy, allylthio and benzoyl, especially methyl.

Suitably, R²², R²³ and R²⁴ are independently selected from hydrogen, halogen, nitro, amino and C₁₋₆ alkyl. Ideally, at least one of R²², R²³ and R²⁴ is other than hydrogen. Preferably, R²³ represents hydrogen, one of R²² and R²⁴ represents halogen or nitro, and the other of R²² and R²⁴ represents hydrogen, halogen or nitro. In a particular embodiment, R²² and R²³ each represents hydrogen and R²⁴ represents halogen, especially chlorine.

Specific compounds within the scope of the present invention include:

7-chloro-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
4-methoxycarbonylmethyl-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
7-chloro-4-methoxycarbonylmethyl-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
7-chloro-4-ethoxycarbonylmethyl-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;

- 14 -

7-chloro-4-methylaminocarbonylmethyl-3-nitro-2-oxo-
1,2,3,4-tetrahydroquinoline;
7-chloro-3-nitro-2-oxo-4-phenylaminocarbonylmethyl-
1,2,3,4-tetrahydroquinoline;
5 4-benzylaminocarbonylmethyl-7-chloro-3-nitro-2-oxo-
1,2,3,4-tetrahydroquinoline;
7-chloro-4-(N,N-dimethylaminocarbonylmethyl)-3-nitro-2-
oxo-1,2,3,4-tetrahydroquinoline;
7-chloro-4-(N-methyl-N-phenylaminocarbonylmethyl)-3-
10 nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
7-chloro-4-(3-methyl-1,2,4-oxadiazol-5-ylmethyl)-3-nitro-
2-oxo-1,2,3,4-tetrahydroquinoline;
and salts and prodrugs thereof.

The present invention also provides
15 pharmaceutical compositions comprising at least one of
the novel compounds according to the invention in
association with a pharmaceutically acceptable carrier.

The pharmaceutical compositions of this
invention are preferably in unit dosage forms such as
20 tablets, pills, capsules, powders, granules, sterile
parenteral solutions or suspensions, or suppositories,
for oral, parenteral or rectal administration.
Alternatively, the composition may be presented in a form
suitable for once-weekly or once-monthly administration;
25 for example, an insoluble salt of the active compound,
such as the decanoate salt, may be adapted to provide a
depot preparation for intramuscular injection. For
preparing solid compositions such as tablets, the
principal active ingredient is mixed with a
30 pharmaceutical carrier, e.g. conventional tableting
ingredients such as corn starch, lactose, sucrose,
sorbitol, talc, stearic acid, magnesium stearate,
dicalcium phosphate or gums, and other pharmaceutical
diluent, e.g. water, to form a solid preformulation

- 15 -

composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

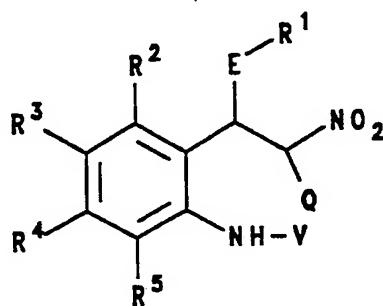
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for

- 16 -

aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

5 In the treatment of neurodegeneration, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

10 The compounds according to the invention may be prepared by a process which comprises the cyclisation of a compound of formula III:



(III)

wherein R¹, R², R³, R⁴, R⁵ and E are as defined above, Q represents a reactive carboxylate moiety, and V represents hydrogen or an amino-protecting group; accompanied, where necessary, by removal of the amino-protecting group V.

25 Suitable values for the reactive carboxylate moiety Q include esters, for example C₁₋₄ alkyl esters; acid anhydrides, for example mixed anhydrides with C₁₋₄ alkanolic acids; acid halides, for example acid chlorides; orthoesters; and primary, secondary and tertiary amides.

30 Preferably, the group Q represents methoxycarbonyl or ethoxycarbonyl.

- 17 -

Suitable examples of amino-protecting groups for the substituent V include carboxylic acid groups such as acetyl, chloroacetyl, trifluoroacetyl, formyl, benzoyl, phthaloyl, phenylacetyl or pyridinecarbonyl; acid groups derived from carbonic acid such as ethoxycarbonyl, benzyloxycarbonyl, t-butoxycarbonyl, biphenylisopropoxycarbonyl, p-methylbenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-phenylazobenzyloxycarbonyl, p-(p'-methoxyphenylazo)-benzyloxycarbonyl or t-amylloxycarbonyl; acid groups derived from sulphonic acid, e.g. p-toluenesulphonic acid; and other groups such as benzyl, trityl, o-nitrophenylsulphenyl or benzylidene.

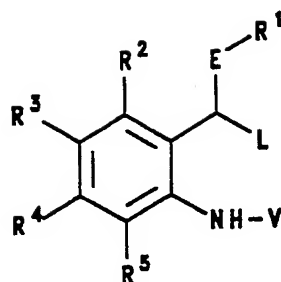
A preferred amino-protecting group is acetyl. The removal of the amino-protecting group present in the resultant compound may be effected by an appropriate procedure known from the art, depending upon the nature of the protecting group employed.

The cyclisation of the compound of formula III is advantageously effected under conditions which afford concomitant removal of the nitrogen-protecting group V, if present. For example, where V represents acetyl and Q is an ethoxycarbonyl group, the reaction is conveniently carried out in methanolic hydrochloric acid at the reflux temperature of the solvent.

The intermediates of formula III above may conveniently be prepared by reacting a compound of formula $Q-CH_2-NO_2$ with a compound of formula IV:

30

- 18 -



(IV)

10 wherein R^1 , R^2 , R^3 , R^4 , R^5 , E , Q and V are as defined above, and L represents a leaving group; in the presence of a strong base.

The leaving group L is suitably a halogen atom, e.g. chlorine.

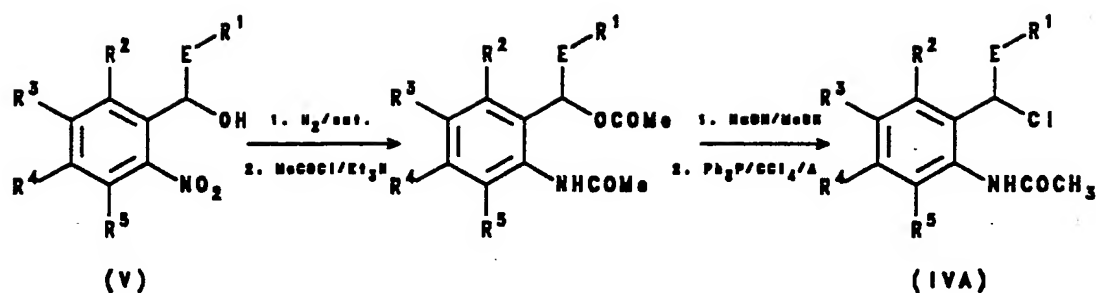
15 Where, for example, the reagent of formula $\text{Q-CH}_2\text{-NO}_2$ is ethyl nitroacetate, the strong base employed will advantageously be sodium ethoxide and the reaction will conveniently be carried out in N,N -dimethylformamide at a temperature in the region of 60°C . Alternatively,

20 where appropriate, the sodium salt of the reagent of formula $\text{Q-CH}_2\text{-NO}_2$ may advantageously be prepared prior to commencement of the reaction and stored until required.

A typical procedure for the preparation of the intermediates of formula IV is illustrated by the

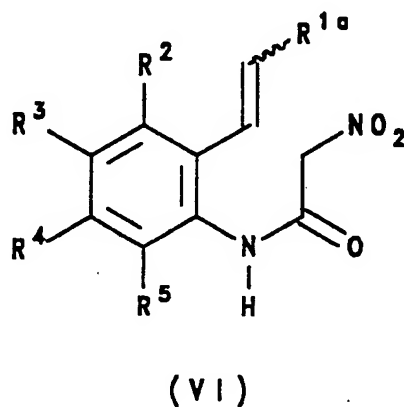
25 following scheme:

- 19 -



wherein R^1 , R^2 , R^3 , R^4 , R^5 , E, Q and V are as defined above.

15 In an alternative process, the compounds according to the invention in which E is a methylene group and the substituent R^1 is an electron-withdrawing group may be prepared by intramolecular Michael cyclisation of a compound of formula VI:



30 wherein R^2 , R^3 , R^4 and R^5 are as defined above, and R^{1a} is an electron-withdrawing group corresponding to the substituent R^1 as defined above.

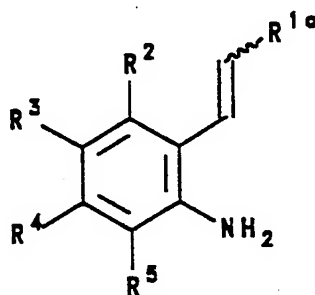
The electron-withdrawing substituent R^{1a} suitably represents a group of formula $-CO_2R^a$ or $-CONR^aR^b$, wherein R^a and R^b are as defined above, or a five-membered heteroaromatic ring containing the ring

- 20 -

atoms W and Z as defined above, provided that the heteroaromatic ring in question has electron-withdrawing properties. A heteroaromatic ring of particular note in this regard is the optionally 3-substituted 1,2,4-oxadiazol-5-yl ring.

The cyclisation of the compound of formula VI is suitably effected in the presence of a strong base such as a sodium alkoxide, e.g. sodium methoxide, ideally in the corresponding alkanol, e.g. methanol.

The intermediates of formula VI above may conveniently be prepared from the corresponding aniline derivatives of formula VII:



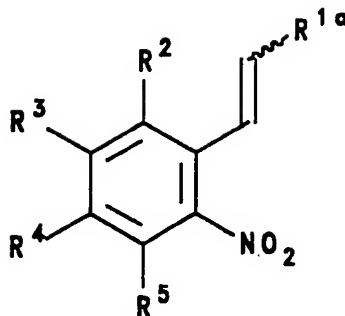
(VII)

wherein R^2 , R^3 , R^4 , R^5 and R^{1a} are as defined above; by treatment with phosgene in the presence of triethylamine, followed by treatment of the product thereby obtained with nitromethane in the presence of a strong base such as potassium t-butoxide.

Both steps of the above procedure are suitably carried out in tetrahydrofuran as solvent, conveniently at a temperature in the region of 0°C .

The intermediates of formula VII above may conveniently be prepared by reduction of the corresponding nitro compounds of formula VIII:

- 21 -



(VIII)

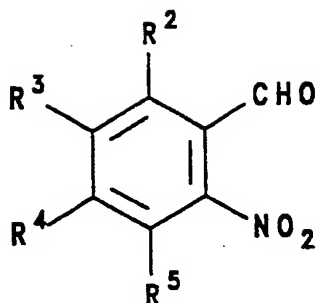
wherein R², R³, R⁴, R⁵ and R^{1a} are as defined above.

A suitable reducing agent is zinc/acetic acid in ethanol.

Where appropriate, the desired intermediate of
 15 formula VII or VIII may be obtained from a precursor
 compound of formula VII or VIII respectively by suitable
 functional group interconversion. For example, a
 compound of formula VIII wherein R^{1a} represents a group
 of formula -CONR^aR^b may be prepared from a compound of
 20 formula VIII wherein R^{1a} represents -CO₂R^a by
 saponification followed by condensation with an
 appropriate amine H-NR^aR^b. Similarly, a compound of
 formula VII wherein R^{1a} represents an optionally 3-
 substituted 1,2,4-oxadiazol-5-yl substituent may be
 25 prepared by reacting a compound of formula VII wherein
 R^{1a} represents -CO₂R^a with a compound of formula
 A¹-C(=NOH)NH₂ in the presence of sodium hydride, in a
 suitable solvent such as tetrahydrofuran.

The compounds of formula VIII wherein R^{1a}
 30 represents a group of formula -CO₂R^a may be prepared by
 Wittig reaction between a reagent of formula Ph₃P=CHCO₂R^a
 and an aldehyde of formula IX:

- 22 -



(IX)

wherein R², R³, R⁴, R⁵ and R^a are as defined above.

The Wittig reaction is conveniently effected by heating the reagents together at reflux temperature in a solvent such as toluene.

15 Where they are not commercially available, the intermediates of formulae V and IX above may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from the art.

20 It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I, for example by methods analogous to those described above
25 for the intermediates of formula VIII.

 Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as
30 preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques,

- 23 -

such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and
5 regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it
10 may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973;
15 and T.W. Greene & P.G.M. Wutts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the
20 preparation of compounds according to the invention.

The compounds useful in this invention potentially and selectively block responses to NMDA and/or AMPA in a brain slice from rat cortex, and inhibit the binding of agonists and antagonists to the strychnine-insensitive
25 site present on the NMDA receptor and/or AMPA binding to rat forebrain membranes.

Cortical Slice Studies

The effects of compounds of the invention on
30 responses to NMDA and AMPA were assessed using the rat cortical slice as described by Wong et al., Proc. Natl. Acad. Sci. USA, 1986, 83, 7104. The apparent equilibrium constant (K_b) was calculated from the righthand shift in the NMDA or AMPA concentration-response curves produced

- 24 -

by the compound under test. Of those compounds of the accompanying Examples which were tested, all were found to possess a K_b value in response to NMDA of below 150 μ M. The compound of Example 2 was tested and was found to possess a K_b value in response to AMPA of below 150 μ M.

Binding Studies

The ability of test compounds to displace either ^3H -glycine binding or ^3H -L-689,560 (trans-2-carboxy-5,7-dichloro-4-phenylaminocarbonylamino-1,2,3,4-tetrahydroquinoline) binding to the strychnine-insensitive site present on the NMDA receptor of rat forebrain membranes was determined. ^3H -Glycine binding was measured by the method of Donald et al., Proceedings of The British Pharmacological Society, University of Nottingham, September 1988, Abstract P122. ^3H -L-689,560 binding was measured by the method of Grimwood et al., Proceedings of the British Pharmacological Society, July 1991, Abstract C78. The concentration of the compounds of the accompanying Examples required to displace 50% of the specific binding of either tritiated ligand (IC_{50}) is below 50 μ M in each case.

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- 25 -

EXAMPLE 17-Chloro-4-methoxycarbonylmethyl-3-nitro-3,4-dihydroquinolin-2-one

5

a) Trans-4-Chloro-2-nitro-1-(2-methoxycarbonylethenyl)-benzene

4-Chloro-2-nitrobenzaldehyde (5g, 0.027M) was dissolved in
10 toluene (150ml) with methyl (triphenylphosphoranylidene)
acetate (9.91g, 1.1 molar equivalents) and heated under reflux
for 1h. The reaction mixture was concentrated under vacuum
and the residue was purified by chromatography on silica gel
using dichloromethane as eluent to give the required compound
15 (6.4g, 98%) as a solid. δ (360MHz, CDCl_3) 3.83 (3H, s, CH_3),
6.36 (1H, d, $J = 15.9\text{Hz}$, $\text{CH}_A=\text{CH}_B$), 7.58 (1H, d, $J = 8.4\text{Hz}$, 6-
H), 7.63 (1H, dd, $J = 8.4$ and 2.0Hz , 5-H), 8.04 (1H, d, $J = 2.0\text{Hz}$,
3-H), 8.05 (1H, d, $J = 8.4\text{Hz}$, $\text{CH}_A=\text{CH}_B$); MS (EI) m/e 241 [M^+].

20

b) Trans-2-Amino-4-chloro-1-(2-methoxycarbonylethenyl)-benzene

The product from Example 1a (2g, 0.0083M) was dissolved
in glacial acetic acid (20ml) and absolute ethanol (20ml) then
25 zinc dust (2g) was added and the reaction mixture was heated at
60°C for 4h under an atmosphere of nitrogen. After cooling, the

- 26 -

5 mixture was filtered and the solution was concentrated under vacuum. The residue was dissolved in ethyl acetate (200ml) and washed with dilute sodium hydroxide solution, then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue on silica gel, using 20% ethyl acetate in hexane as the eluent, gave the required compound as a yellow solid (1.25g, 71%). δ (360MHz, CDCl_3) 3.80 (3H, s, CH_3), 4.02 (2H, br s, NH_2), 6.32 (1H, d, $\underline{J} = 15.8\text{Hz}$, $\text{CH}_\text{A}=\text{CH}_\text{B}$), 6.70 (1H, d, $\underline{J} = 1.9\text{Hz}$, H-3), 6.73 (1H, dd, $\underline{J} = 8.3$ and 1.9Hz , 5-H), 7.28 (1H, d, $\underline{J} = 8.3\text{Hz}$, 6-H), 7.72 (1H, d, $\underline{J} = 15.8\text{Hz}$, $\text{CH}_\text{A}=\text{CH}_\text{B}$); MS (EI) m/e 211 [M^+].

c) Trans-4-Chloro-2-nitromethylcarbonylamino-1-methoxycarbonyl ethenyl-benzene

15

The product from Example 1b (1g, 0.00473M) was dissolved in dry tetrahydrofuran (100ml) with triethylamine (1.38ml, 0.0099M) cooled to 0°C and phosgene (3.1ml of a 1.93 molar solution in toluene, 0.006M) was added. After stirring at 0°C for 20 minutes a preformed solution of nitromethane anion (nitromethane (1.3ml, 0.024M) in tetrahydrofuran (80ml) at 0°C with 26ml of 1 molar potassium tertiary butoxide solution in tetrahydrofuran) was added by cannula. After stirring at 0°C for 1h, the reaction mixture was poured into ice-cold hydrochloric acid and extracted into diethyl ether (3 x 100ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo and the residue was purified by

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- 27 -

trituration with diethyl ether to give the required compound as a white solid (0.56g, 40%); δ (360MHz, DMSO) 3.74 (3H, s, CH₃), 5.63 (2H, s, CH₂NO₂), 6.66 (1H, d, J = 15.8Hz, CH_A=CH_B), 7.36 (1H, dd, J = 8.6 and 1.9Hz, 5-H), 7.65 (1H, d, J = 1.9Hz, 3-H), 7.79 (1H, d, J = 15.8Hz, CH_A=CH_B), 7.89 (1H, d, J = 8.6Hz, 6-H); MS (EI) m/e 298 [M⁺].

d) 7-Chloro-4-methoxycarbonylmethyl-3-nitro-3,4-dihydroquinolin-2-one

10

The product from Example 1c (0.54g, 0.00181M) was dissolved in dry methanol (100ml) and sodium methoxide (generated by dissolving 80% sodium hydride (0.163g, 3 molar equivalents) in dry methanol (30ml)) was added. The reaction mixture was stirred at room temperature for 14h then methanol that had been saturated with hydrogen chloride (100ml) was added and the solvents were removed under vacuum. The residue was dissolved in ethyl acetate (100ml) and extracted with saturated potassium carbonate solution (2 x 100ml). The combined aqueous layers were washed with diethyl ether (2 x 100ml) then acidified to pH 1 with concentrated hydrochloric acid and extracted into ethyl acetate (2 x 100ml), dried (Na₂SO₄), filtered and concentrated in vacuo. The residue obtained was triturated with diethyl ether and collected by filtration to give the title compound as a white solid; m.p. = 135°C (0.077g, 14%); δ (360MHz, DMSO) (9.2:1 mixture of epimers) 2.64 (1H, dd, J = 16.6 and 7.4Hz, CH_AH_BCH_C), 2.86

- 28 -

(1H, dd, $J = 16.6$ and 5.5Hz , $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_\text{C}$), 3.60 (3H, s, CH_3 , major epimer), 3.63 (3H, s, CH_3 , minor epimer), 4.12 (1H, m, $\text{CH}_\text{A}\text{CH}_\text{B}\text{CH}_\text{C}$), 5.78 (1H, d, $J = 6.2\text{Hz}$, CHNO_2 , major epimer), 5.87 (1H, d, $J = 5.0\text{Hz}$, CHNO_2 , minor epimer), 6.98 (1H, d, $J = 1.9\text{Hz}$, 8-H), 7.09 (1H, dd, $J = 8.6$ and 1.9Hz , 6-H), 7.19 (1H, d, $J = 8.6\text{Hz}$, minor epimer), 7.26 (1H, d, $J = 8.6\text{Hz}$, 5-H, major epimer); MS (EI) m/e 298 $[\text{M}^+]$. Found: C, 48.10; H, 3.79; N, 9.16. $\text{C}_{12}\text{H}_{11}\text{ClN}_2\text{O}_5$ requires C, 48.26; H, 3.71; N, 9.38%.

EXAMPLE 2

7-Chloro-3-nitro-3,4-dihydroquinolin-2-one

a) 5-Chloro-2-hydroxymethyl-acetanilide

15

4-Chloro-2-nitrobenzyl alcohol (25.42g, 0.136M) was dissolved in methanol (1000ml) then 5% platinum sulphide on carbon catalyst (2g) was added and the reaction mixture was shaken under a 50 p.s.i. atmosphere of hydrogen for 18h. The mixture was filtered, concentrated under vacuum then redissolved in dichloromethane (1000ml) with triethylamine (41.8ml, 0.3M) and cooled to 0°C . Acetyl chloride (21.3ml, 0.3M) was added dropwise then the reaction mixture was stirred at room temperature for 14h. The solution was washed with 1N HCl (2 x 500ml) and brine (1 x 500ml) then dried (MgSO_4), filtered and concentrated in vacuo. The residue was dissolved in methanol (500ml) and a solution of sodium hydroxide (6g,

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- 29 -

0.15M) in water (200ml) was added. After stirring at room temperature for 1h, the methanol was removed in vacuo and the aqueous residue was extracted with ethyl acetate (3 x 300ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (1 x 200ml), then brine (1 x 200ml), dried (MgSO_4), filtered and evaporated to give the required compound (24.41g, 90%); δ (360MHz, DMSO) 2.07 (3H, s, CH_3), 4.48 (2H, d, $J = 5.5\text{Hz}$, CH_2OH), 5.36 (1H, t, $J = 5.5\text{Hz}$, CH_2OH), 7.18 (1H, dd, $J = 8.5$ and 1.9Hz , 4-H), 7.40 (1H, d, $J = 8.5\text{Hz}$, 3-H), 7.68 (1H, d, $J = 1.9\text{Hz}$, 6-H), 9.34 (1H, br s, NH).

b) 2-Chloromethyl-5-chloro-acetanilide

The product from Example 2a (2g, 0.01M) and triphenylphosphine (2.62g, 0.01M) were dissolved in carbontetrachloride (50ml) and tetrahydrofuran (50ml) and heated at reflux, under nitrogen, for 2h. The solvents were removed under vacuum and the residue was purified by silica gel chromatography using 20-40% ethyl acetate in hexane as eluent to give the required product (1.16g, 53%) m.p. = 148-154°C dec; δ (360MHz, DMSO) 2.10 (3H, s, CH_3), 4.83 (2H, s, CH_2), 7.23 (1H, dd, $J = 8.5$ and 2.0Hz , 4-H), 7.48 (1H, d, $J = 8.5\text{Hz}$, 3-H), 7.68 (1H, d, $J = 2.0\text{Hz}$, 6-H), 9.56 (1H, br s, NH); MS (EI) m/e 217 [M^+].

- 30 -

c) 5-Chloro-2-((2'-ethoxycarbonyl)2'-nitro)ethyl acetanilide

The product from Example 2b (0.55g, 0.0025M) and the sodium salt of ethylnitroacetate (1.18g, 0.0076M) were dissolved in dry dimethylformamide and heated at 60°C under nitrogen for 1h. The reaction mixture was poured into dilute hydrochloric acid (200ml) and extracted into ethyl acetate (2 x 150ml). The combined organic layers were washed with water (1 x 200ml) and brine (1 x 200ml) then dried (MgSO₄), filtered and concentrated in vacuo to give a brown oil. This was purified by chromatography on silica gel using 30-50% ethyl acetate in hexane as eluent to give the required product as a white solid (0.296g, 38%) δ (360MHz, DMSO) 1.16 (3H, t, J = 7.1Hz, CH₃CH₂O), 2.07 (3H, s, J = CH₃CONH), 3.48 (2H, m, CH_AH_BCH_C), 4.19 (2H, q, J = 7Hz, CH₃CH₂O), 5.83 (1H, dd, J = 8.8 and 6.6Hz, CH_AH_BCH_C), 7.22 (2H, m, 3-H and 4-H), 7.53 (1H, d, J = 1.9Hz, 6-H), 9.54 (1H, br s, NH); MS (EI) m/e 314 [M⁺].

d) 7-Chloro-3-nitro-3,4-dihydroquinolin-2-one

The product from Example 2c (0.25g, 0.0008M) was dissolved in methanol (10ml) that had been presaturated with hydrogen chloride and heated under reflux for 1h then concentrated under vacuum. The residue was recrystallised from ethyl acetate/hexane to give the required compound as a white solid (0.083g, 46%) m.p. = 194-197°C; δ (360MHz, DMSO)

- 31 -

3.58 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_\text{C}\text{NO}_2$), 5.87 (1H, dd, $\underline{J} = 10.0$ and 6.8Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_\text{C}\text{NO}_2$), 6.94 (1H, d, $\underline{J} = 1.9\text{Hz}$, H=8), 7.07 (1H, dd, $\underline{J} = 8.1$ and 1.8Hz, 6-H), 7.29 (1H, d, $\underline{J} = 8.1\text{Hz}$, 5-H), 10.99 (1H, br s, NH); MS (EI) m/e 226 [M^+]; Found: C, 48.05; H, 2.99; N, 11.85. $\text{C}_9\text{H}_7\text{ClN}_2\text{O}_3$ requires C, 47.77; H, 3.18; N, 12.22%.

EXAMPLE 3

10 7-Chloro-4-[(N-methyl)phenylaminocarbonyl]methyl-3-nitro-3,4-dihydroquinolin-2-one. Sodium salt.

15 a. Cis and trans-4-chloro-2-nitro-1-(2-carboxyethenyl)benzene.

15 4-Chloro-2-nitrobenzaldehyde (5g, 0.027m) was dissolved in toluene (150ml) with methyl (triphenylphosphoranylidene) acetate (9.91g, 1.1 molar equivalents) and heated under reflux for 1h. The reaction mixture was concentrated under vacuum and the residue was purified by chromatography on silica gel using dichloromethane as eluent to give a solid (Example 1a). This was dissolved in 50% aqueous acetone (500ml) with sodium hydroxide (3.5g) and the solution was stirred at room temperature for 2h. The acetone was removed under vacuum and the aqueous residue was acidified to pH 1 using concentrated HCl then extracted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated in vacuo to give the required product (5.5g, 90%). m.p. = 165°C.(sub); δ (250MHz,

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- 32 -

CDCl) 6.15 (1H, d, $J = 11.9\text{Hz}$, cis $\text{CH}_A = \text{CH}_B$), 6.35 (1H, d, $J = 15.7\text{Hz}$, trans ($\text{CH}_A = \text{CH}_B$), 7.45 (1H, d, $J = 11.9\text{Hz}$, cis $\text{CH}_A = \text{CH}_B$), 7.34-7.64 (4H, m cis 5-H and 6-H, trans 5-H and 6-H), 8.06 (1H, d, $J = 2.0\text{Hz}$, H-3), 8.17 (1H, d, $J = 2.0\text{Hz}$, H-3), 8.13 (1H, d, $J = 15.7\text{Hz}$, trans $\text{CH}_A = \text{CH}_B$); MS (EI) m/e 227 [M^+].

b. Trans-4-chloro-2-nitro-2-(2-[(N-methyl)phenylaminocarbonyl]ethenyl)benzene

The product from Example 3a (5g, 0.022m) was dissolved in tetrahydrofuran (200ml) with triethylamine (9.1m, 3 molar equivalents), 1-hydroxybenzotriazole (4.46g, 1.5 molar equivalents) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.5g, 1.5 molar equivalents) and stirred at room temperature for 14h. The solvent was evaporated under vacuum and the residue was dissolved in ethyl acetate (500ml) and washed with 0.5 N citric acid solution (3 x 200ml), saturated sodium hydrogen carbonate solution (3 x 200ml) and brine (1 x 200ml). The organic layer was dried (Na_2SO_4), filtered and concentrated under vacuum to give a residue which was purified by silica gel chromatography using 30% ethyl acetate in hexane as eluent to give the required product as a white solid (3.97g, 57%). m.p. = 99-101°C; δ (360MHz, DMSO) 3.32 (3H, s, N- CH_3), 6.39 (1H, d, $J = 15.9\text{Hz}$), 7.14-7.82 (8H, m, H-5, H-6 and Ph), 8.12 (1H, d, $J = 1.9\text{Hz}$, 3-H); MS EI m/e 316 [M^+].

- 33 -

c. Trans-2-amino-4-chloro-1-(2-[(N-methyl)phenylaminocarbonyl]ethenyl)benzene

The product from Example 3b (3.9g, 0.0123m) was dissolved
5 in ethanol (40ml) with glacial acetic acid (40ml) and zinc dust
(5g) was added. The reaction mixture was heated at 60°C for 3h
then filtered and the solvents removed under vacuum. The
residue was in hexane as eluent to give the required product as
a yellow oil (2.18g, 54%). δ (360MHz, DMSO) 3.30 (3H, s,
10 NCH_3), 5.71 (2H, br, s, NH_2), 6.19 (1H, d, $\underline{J} = 15.7\text{Hz}$, $\text{CH}_\text{A} =$
 CH_B), 6.44 (1H, dd, $\underline{J} = 8.4$ and 2.0Hz , 5-H), 6.69 (1H, d, $\underline{J} =$
 2.0Hz , 3-H), 6.93 (1H, d, $\underline{J} = 8.4\text{Hz}$, 6-H), 7.30-7.49 (5H, m, Ph),
7.64 (1H, d, $\underline{J} = 15.7\text{Hz}$, $\text{CH}_\text{A} = \text{CH}_\text{B}$); MS (EI) m/e 286 [M^+].

15 d. 7-Chloro-4-[(N-methyl)phenylaminocarbonyl]methyl-3-nitro-3,4-dihydroquinolin-2-one. Sodium salt.

Treatment of the product from Example 3c under the
conditions described in Examples 1c and 1d gave the title
20 compound which was isolated as its sodium salt by dissolution
in a solution of sodium methoxide in methanol, concentration to
a small volume and collection by filtration. m.p. = 240°C (dec).
 δ (360MHz, D_2O) 2.48 (1H, dd, $\underline{J} = 13.4$ and 5.2Hz ,
 $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_\text{C}$), 2.52 (1H, dd, $\underline{J} = 13.4$ and 8.6Hz , $\text{CH}_\text{A}\text{CH}_\text{B}\text{CH}_\text{C}$),
25 3.13 (3H, s, CH_3), 4.66 (1H, dd, $\underline{J} = 8.6$ and 5.2Hz ,
 $\text{CH}_\text{A}\text{CH}_\text{B}\text{CH}_\text{C}$), 6.74 (2H, m, aromatics), 6.88 (1H, d, $\underline{J} = 1.8\text{Hz}$,
8-H), 7.02 (1H, d, $\underline{J} = 8.2\text{Hz}$, 5-H), 7.06 (1H, dd, $\underline{J} = 8.2$ and

- 34 -

1.8Hz, 6-H), 7.36 (3H, m, aromatics); MS (FAB m/e 396 [MH]⁺;
Found C, 51.67; H, 3.95, N, 9.84. C₁₈H₁₅ClN₃O₄Na. 1.2H₂O
requires C, 51.80; H, 4.20; N, 10.07%.

EXAMPLE 4

5

7-Chloro-4(N,N-dimethylaminocarbonyl)methyl-3-nitro-3,4-dihydroquinolin-2-one

10 The title compound as prepared as for Example 3, parts a, b
(using dimethylamine hydrochloride in place of N-methylaniline), and c; and Example 1, parts c and d, to yield the
crude product which was recrystallised from ethyl acetate
hexane to give a white solid. m.p. = 210-211°C (decomp).
15 Found: C, 50.17; H, 4.57; N, 13.08%. C₁₃H₁₄ClN₃O₄ requires
C, 50.09; H, 4.53; N, 13.48%. δ (360MHz, DMSO) (11:1 mixture
of epimers) 2.69 (1H, dd, J = 16.6 and 7.4Hz, CH_AH_BCH_C) 2.77-
2.85 (7H, m, CH_ACH_BCH_C, N(CH₃)₂), 4.14 (1H, m,
CH_AH_BCH_C) 5.74 (1H, d, J = 6.2Hz, CHNO₂ major epimer,
20 5.80 (1H, d, J = 5.0Hz, CHNO₂ minor epimer), 6.97 (1H, d, J =
1.9Hz, 8-H), 7.07 (1H, dd, J = 8.6 and 1.9Hz, 6-H), 7.20 (1H, m,
5-H); MS (CI⁺) m/e 312 [M⁺ H].

- 35 -

EXAMPLE 5Tablet Preparation

5 Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0mg,
respectively of the following compounds are prepared as
illustrated below:

10 7-Chloro-4-methoxycarbonylmethyl-3-nitro-3,4-
dihydroquinolin-2-one

7-Chloro-3-nitro-3,4-dihydroquinolin-2-one

15 7-Chloro-4-[(N-methyl)phenylaminocarbonyl]methyl-3-nitro-
3,4-dihydroquinolin-2-one. Sodium salt.

7-Chloro-4(N,N-dimethylaminocarbonyl)methyl-3-nitro-3,4-
dihydroquinolin-2-one

20

TABLE FOR DOSES CONTAINING FROM
1-25MG OF THE ACTIVE COMPOUND

		Amount-mg		
25	Active Compound	1.0	2.0	25.0
	Microcrystalline cellulose	49.25	48.75	37.25
	Modified food corn starch	49.25	48.75	37.25
	Magnesium stearate	0.50	0.50	0.50

- 36 -

TABLE FOR DOSES CONTAINING FROM
26-100MG OF THE ACTIVE COMPOUND

	Amount-mg		
5			
Active Compound	26.0	50.0	100.0
Microcrystalline cellulose	52.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	0.39	0.75	1.5

10

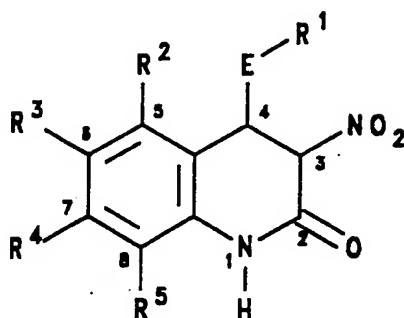
All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The

15 resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active ingredient per tablet.

- 37 -

CLAIMS:

1. A compound of formula I, or a salt or
 5 prodrug thereof:

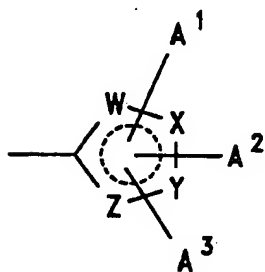


(I)

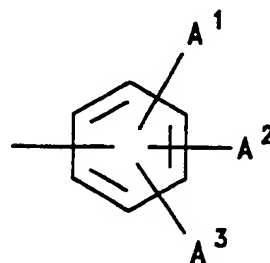
wherein

E represents a bond or a straight or branched
 alkylene chain containing from 1 to 4 carbon atoms;

20 R^1 represents hydrogen, $-OR^a$, $-NR^aR^b$, $-CO_2R^a$,
 $-CONR^aR^b$ or a group of formula



or



30 in which the broken circle represents two non-adjacent
 double bonds in any position in the five-membered ring;

W, X, Y and Z independently represent oxygen,
 sulphur, nitrogen or carbon, provided that no more than
 one of W, X, Y and Z represents oxygen or sulphur, at

- 38 -

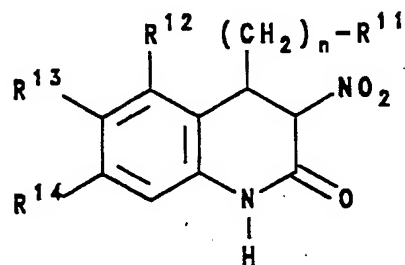
least one of W, X, Y and Z represents carbon and at least one of W, X, Y and Z is other than carbon;

A^1 , A^2 and A^3 represent one, two or three substituents (not exceeding the maximum number permissible by the disposition of heteroatoms in the five-membered ring), which substituents are independently selected from hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; or A^1 and A^2 or A^2 and A^3 together represent the residue of an aromatic or heteroaromatic ring;

R^2 , R^3 , R^4 and R^5 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; or R^2 and R^3 , R^3 and R^4 or R^4 and R^5 together represent the residue of an aromatic or heteroaromatic ring; and

R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

2. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:



(IIA)

- 39 -

wherein

n is zero, 1, 2 or 3;

R¹¹ represents hydrogen, -OR¹⁶, -NR¹⁶R¹⁷,
-CO₂R¹⁶ or -CONR¹⁶R¹⁷;

5 R¹², R¹³ and R¹⁴ independently represent
hydrogen, halogen, cyano, trifluoromethyl, nitro,
hydroxy, amino, carboxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆
alkylthio or C₂₋₆ alkoxy carbonyl; and

10 R¹⁶ and R¹⁷ independently represent hydrogen,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl,
C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl or
heteroaryl(C₁₋₆)alkyl, any of which groups may be
optionally substituted.

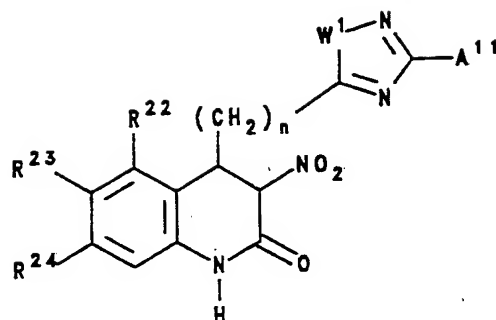
15 3. A compound as claimed in claim 2 wherein n
is zero and R¹¹ is hydrogen.

20 4. A compound as claimed in claim 2 wherein n
is 1 and R¹¹ is methoxy, dimethylamino, methoxycarbonyl,
ethoxycarbonyl, methylaminocarbonyl, phenylaminocarbonyl,
benzylaminocarbonyl, dimethylaminocarbonyl or N-methyl-N-
phenylaminocarbonyl.

25 5. A compound as claimed in claim 1
represented by formula IIB, and salts and prodrugs
thereof:

30

- 40 -



(11B)

wherein

n is zero, 1, 2 or 3;

W^1 represents oxygen or sulphur;

A^{11} represents hydrogen, halogen, cyano, trifluoromethyl, nitro, hydroxy, amino, carboxy, C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, C₃-7 cycloalkyl, C₃-7 cycloalkyl(C₁-6)alkyl, aryl, aryl(C₁-6)alkyl, C₁-6 alkoxy, C₂-6 alkenyloxy, C₁-6 alkylthio, C₂-6 alkenylthio, C₂-6 alkylcarbonyl, arylcarbonyl or C₂-6 alkoxy carbonyl; and

R^{22} , R^{23} and R^{24} independently represent hydrogen, halogen, cyano, trifluoromethyl, nitro, hydroxy, amino, carboxy, C₁-6 alkyl, C₁-6 alkoxy, C₁-6 alkylthio or C₂-6 alkoxy carbonyl.

6. A compound as claimed in claim 5 wherein n is 1, W^1 is oxygen and A^{11} is methyl.

7. A compound as claimed in claim 1 selected from:
7-chloro-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
4-methoxycarbonylmethyl-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;

- 41 -

- 7-chloro-4-methoxycarbonylmethyl-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
7-chloro-4-ethoxycarbonylmethyl-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
5 7-chloro-4-methylaminocarbonylmethyl-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
7-chloro-3-nitro-2-oxo-4-phenylaminocarbonylmethyl-1,2,3,4-tetrahydroquinoline;
4-benzylaminocarbonylmethyl-7-chloro-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
10 7-chloro-4-(N,N-dimethylaminocarbonylmethyl)-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
7-chloro-4-(N-methyl-N-phenylaminocarbonylmethyl)-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
15 7-chloro-4-(3-methyl-1,2,4-oxadiazol-5-ylmethyl)-3-nitro-2-oxo-1,2,3,4-tetrahydroquinoline;
and salts and prodrugs thereof.

8. A pharmaceutical composition comprising a
20 compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier or excipient.

9. The use of a compound as claimed in any
25 one of claims 1 to 7 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions which require the administration of a non-competitive antagonist of NMDA receptors.

30 10. The use of a compound as claimed in any one of claims 1 to 7 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions which require the administration of an antagonist of AMPA receptors.

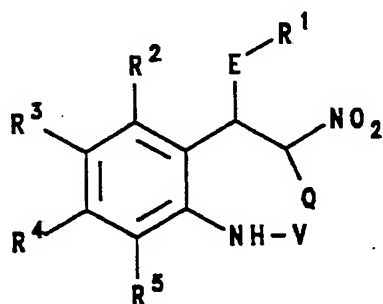
- 42 -

11. A process for the preparation of a compound as claimed in any one of claims 1 to 7 which comprises:

5

(A) the cyclisation of a compound of formula

III:



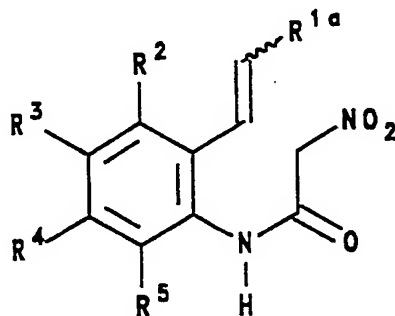
(III)

wherein R¹, R², R³, R⁴, R⁵ and E are as defined in claim 1, Q represents a reactive carboxylate moiety, and V represents hydrogen or an amino-protecting group; accompanied, where necessary, by removal of the amino-protecting group V; or

20

(B) intramolecular Michael cyclisation of a compound of formula VI; or

25



(VI)

- 43 -

wherein R^2 , R^3 , R^4 and R^5 are as defined in claim 1, R^{1a} is an electron-withdrawing group corresponding to the substituent R^1 as defined in claim 1; and

5 (C) where appropriate, converting a compound of formula I initially obtained into a further compound of formula I using methods known per se.

10 12. A compound as claimed in any one of claims 1 to 7 for use in therapy.

15 13. A method for the treatment and/or prevention of conditions which require the administration of a selective non-competitive antagonist of NMDA receptors, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof.

20 14. A method for the treatment and/or prevention of conditions which require the administration of an antagonist of AMPA receptors, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in
25 claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof.

INTERNATIONAL SEARCH REPORT

PCT/GB 93/00013

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D215/22; A61K31/47; C07D413/06

II. FIELDS SEARCHEDMinimum Documentation Searched⁷

Classification System

Classification Symbols

Int.Cl. 5

C07D

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸**III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹**

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 459 561 (MERCK SHARP & DOHME LTD.) 4 December 1991 see claims	1,8,9
A	EP,A,0 398 283 (MERRELL DOW PHARMACEUTICALS INC.) 22 November 1990 see claims	1,8,9

¹⁰ Special categories of cited documents:

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- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

26 MARCH 1993

Date of Mailing of this International Search Report

14. 04. 93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

VAN BIJLEN H.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300013
SA 69522

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0459561	04-12-91	AU-A- 7807591	05-12-91
		JP-A- 4235970	25-08-92
EP-A-0398283	22-11-90	AU-B- 626418	30-07-92
		AU-A- 5491490	22-11-90
		CA-A- 2016908	16-11-90
		CN-A- 1047292	28-11-90
		JP-A- 3011067	18-01-91
		US-A- 5026700	25-06-91
		US-A- 5112821	12-05-92

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